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Deficits in Auditory Processing Contribute to Impairments in Vocal Affect Recognition in Autism Spectrum Disorders: A MEG Study

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Abstract

Objective—The primary aim of this study was to examine if there is an association between magnetoencephalography-based (MEG) indices of basic cortical auditory processing and vocal affect recognition (VAR) ability in individuals with Autism Spectrum Disorders (ASD).

Method—MEG data were collected from 25 children/adolescents with ASD and 12 control participants using a paired-tone paradigm to measure quality of auditory physiology, sensory gating, and rapid auditory processing. Group differences were examined in auditory processing and vocal affect recognition ability. The relationship between differences in auditory processing and vocal affect recognition deficits was examined in the ASD group.

Results—Replicating prior studies, participants with ASD showed longer M1n latencies and impaired rapid processing compared to control participants. These variables were significantly

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Ethical Standards: All procedures were approved by the Institutional Review Board and were in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. All participants' parents gave informed consent with assent from all participants prior to inclusion in the study.

Conflict of Interest: The authors declare that they have no conflict of interest.

related to VAR, with the linear combination of auditory processing variables accounting for ~30% of the variability after controlling for age and language skills in participants with ASD.

Conclusions—VAR deficits in ASD are typically interpreted as part of a core, higher-order dysfunction of the ‘social brain;’ however, these results suggest they also may reflect basic deficits in auditory processing that compromise the extraction of socially relevant cues from the auditory environment. As such, they also suggest that therapeutic targeting of sensory dysfunction in ASDs may have additional positive implications for other functional deficits.

Keywords

MEG; Autism; Social Cognition; Vocal Affect; Auditory Processing

Impairments in social cognition are defining characteristics of Autism Spectrum Disorder (ASD; American Psychiatric Association, 2013). Social cognition encompasses a broad range of skills that support the extraction and processing of social information from the environment. These skills include affect recognition, empathy, and concepts related to ‘theory-of-mind’, or the ability to see the world from the perspective of another (Adolphs, 2001). Models of social information processing have been developed to describe the orchestration of social cognitive processes involved in social interaction (Crick & Dodge, 1994; Shapiro, Hughes, August, & Bloomquist, 1993). In an effort to define the structure and function of the social brain, there have been several recent studies comparing neuroimaging profiles in neurotypical and ASD subjects (Pelphrey, Adolphs, & Morris, 2004). For the most part, the neurobiological research on social information processing in autism has focused on identifying neurobiological dysfunction in structures that directly support higher-order social skills (e.g., the amygdala, superior temporal and frontal regions, etc.). However, theoretical models of social cognition recognize the importance of early stages of sensory processing, since social cues must first be attended to and encoded by the sensory perceptual system before they can be subjected to analyses of social meaning (Crick & Dodge, 1994; Shapiro et al., 1993).

Examination of how sensory dysfunction might contribute to social-cognitive dysfunction is especially relevant in the study of autism because there is a growing body of evidence indicating that some form of sensory disturbance is present in greater than 70% of individuals with ASD (Adamson, Hare, & Graham, 2006; Greenspan & Wieder, 1997; Mayes & Calhoun, 1999; Tomchek & Dunn, 2007). It is now recognized that there is a relationship between the degree of sensory dysfunction and severity of autism symptomatology (Adamson et al., 2006; Brock, Freuler, Baranek, Watson, & Poe, 2012; Rogers, Hepburn, & Wehner, 2003), and sensory dysfunction has finally been acknowledged as a core diagnostic feature in ASD (DSM-V, American Psychiatric Association, 2013).

Much of the difficulty in social interaction for individuals with ASD is thought to stem from difficulty interpreting social emotional cues, including those in the facial expressions and vocal inflections of another person. Our previous work in children and adolescents with an ASD has demonstrated that among verbal and nonverbal social cognitive skills, deficits in vocal affect recognition ability are strongly associated with parent-rated deficits in complex social behavior (Demopoulos, Hopkins, & Lewine, Under Review). In fact, several studies

have demonstrated evidence of poor vocal affect recognition in individuals with ASD (Golan, Baron-Cohen, & Hill, 2006; Järvinen-Pasley, Peppé, King-Smith, & Heaton, 2008; Lindner & Rosén, 2006), although a few have reported inconsistencies within the ASD group with respect to these deficits. For example, Mazefsky and Oswald (2007) reported performance differences in vocal affect recognition between ASD subtypes, with impaired performance in a high functioning autism group, but not in the group with Asperger's Disorder.

At present, the etiology of autism-related deficits in vocal affect recognition remains unclear. Considerable research has focused on hypotheses related to lack of social motivation or dysfunction in social cognitive systems (Abrams et al., 2013; Aoki et al., 2014; Baron-Cohen et al., 2000; McCann & Peppé, 2003; Pelphrey et al., 2004); however, emerging research suggests that impaired processing of the basic auditory cues of vocalization that convey emotion also may contribute to development of these social cognitive deficits (Globerson, Amir, Kishon-rabin, & Golan, 2014; Lerner, McPartland, & Morris, 2013). This hypothesis is consistent with converging data showing that many children with ASDs have abnormal auditory processing and impaired vocal affective cue recognition, as measured by both behavioral and electrophysiological methods (Baranek, 1999; Bonnel et al., 2003; Dahlgren & Gillberg, 1989; Gillberg & Coleman, 1996; Golan, Baron-Cohen & Hill, 2006; Greenspan & Weider, 1997; Järvinen-Palsey, Peppé, King-Smith & Heaton, 2008; Linder & Rosen, 2006; O'Riordan & Passetti, 2006; Osterling & Dawson, 1994; Rimland & Edelson, 1995; Tecchio et al., 2003; Tomchek, & Dunn, 2007). It is important to determine if anomalies in basic auditory processing contribute to deficits in social perception and social performance in children with ASDs because, if such a relationship exists, it would suggest a new target (auditory processing) for preventive and early intervention strategies aimed at improving social cognition.

Vocal affect cues are believed to be embedded in the amplitude, timing, fundamental frequency (and associated perceived pitch), and/or 'quality' of speech (reflected in the energy distribution of a speaker's frequency spectrum) - factors encoded in the firing patterns of neurons in the primary and secondary auditory cortices. Information on the neuronal activity of auditory cortex can be non-invasively recorded using electroencephalography (EEG) and magnetoencephalography (MEG), and several studies demonstrate clear abnormalities in these signals in autism (Cardy, Flagg, Roberts, Brian, & Roberts, 2005; Edgar et al., 2013; Gage, Siegel, & Roberts, 2003; Gandal et al., 2010; Järvinen-Pasley & Heaton, 2007; Oram Cardy et al., 2005, 2008; Roberts et al., 2010, 2011; Rojas et al., 2011; Schmidt, Rey, Oram Cardy, & Roberts, 2009; Tecchio et al., 2003; Tomcheck & Dunn, 2007; Wilson, Rojas, Reite, Teale, & Rogers, 2007). Reported abnormalities include absent signals, anomalous oscillatory profiles, reduced mis-match signals, impaired rapid auditory processing, and delayed processing components (especially the M100).

Remarkably, to date, only the recent study of Lerner and colleagues (2013) has attempted to related electrophysiological indices of auditory processing and vocal affect recognition. In this study, it was found that shorter N1 latencies (measured by EEG) were associated with better vocal affect recognition. Stimuli in this study were speech sounds, so it remains

unclear whether the relation between abnormalities in auditory processing and deficits in vocal affect recognition is restricted to difficulties processing more complex auditory information such as speech sounds, or whether deficits in processing more basic auditory information also might be associated with difficulty interpreting affect from vocal cues.

Thus, the aim of the present study was to test the hypothesis that difficulties in vocal affect recognition are related to basic problems in auditory processing. Understanding the relationship between sensory dysfunction and core autism symptoms, especially those related to social cognition, may elucidate some of the neurobiological processes that account for the heterogeneity in the clinical presentation of ASD. It is important to determine if anomalies in basic auditory processing contribute to deficits in social perception (and resultant deficits in social response) in children with ASD because, if such a relationship exists, it would suggest a new target (auditory processing) for preventive and early intervention strategies aimed at improving social cognitive skill development.

For this study, vocal affect recognition was assessed via a composite score of the adult and child paralinguistic subtests of the Diagnostic Analysis of Nonverbal Accuracy-Second Edition (DANVA-2). MEG was used to evaluate cortical processing of rapidly presented auditory stimuli. One of the most robust findings in the ASD electrophysiology literature is a delayed M1n response, especially to low frequency sounds (M1n is the neuromagnetic correlate of the EEG recorded N100 response, Oram Cardy, Flagg, Roberts, & Roberts, 2005; Roberts et al., 2008, 2010; Edgar et al., 2014). In this study we explored the relationship between DANVA performance, and MEG measures of M1n amplitude and latency, plus additional composite variables assessing auditory sensory gating and rapid auditory processing. Sensory gating and rapid auditory processing are additional variables of particular interest because they have been shown in other studies to relate to sensory filtering (Oranje, Lahuis, van Engeland, Jan van der Gaag, & Kemner, 2013; Potter, Summerfelt, Gold, & Buchanan, 2006) and language abilities (Roberts et al., 2008), respectively, two likely contributors to vocal affect recognition. Specifically it was hypothesized that, even after controlling for age and language ability, there would be a significant relationship between anomalies in the neurobiological mechanisms that support auditory processing and deficits in vocal affect recognition. This study is the first to use MEG to assess auditory evoked fields in relation to specific social-emotional skills in children and adolescents with autism across a broad range of functioning.

Methods

Participants

The initial sample included 52 children and adolescents, including 15 typically developing participants and 37 participants with an ASD. All participants were between the ages of 5-18 years. Individuals diagnosed with Fragile-X, Tuberous Sclerosis or any comorbid neurological conditions were excluded. Criteria for inclusion were: (1) DSM-IV-TR diagnosis of Autistic Disorder, Asperger's Syndrome, or Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS), as supported by data on the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) for the ASD group, (2) age within the

specified range of 5-18 years, and (3) ability to comprehend instructions for the vocal affect recognition task.

Prior evidence suggests that low functioning individuals with ASD show specific auditory processing abnormalities (Tecchio et al., 2003), but low functioning participants are often excluded from brain research on the ASDs. Given the dimensional approach to our research question, it was important to include as representative a sample of individuals on the autism spectrum as possible. Therefore, in an effort to include lower functioning participants while also ensuring comprehension of the DANVA-2 task, participants who did not score significantly greater than chance were excluded from subsequent analyses. To determine the cutoff score for inclusion, first the number of correct responses predicted by chance was calculated for the 48 DANVA items with four response choices, indicating that a score of 12 correct responses could be attributed to chance alone. The minimum number of correct responses that was significantly better than chance was 19, $z=2.05$, $p=.04$, and thus a minimum raw score of 19 on the DANVA-2 was used to confirm task comprehension and those scoring below 19 correct responses were excluded. Seven participants (all with an ASD diagnosis) were thereby excluded from further analyses due to chance performance on the DANVA. As described below, eight additional participants (five from the ASD group and three from the control group) were excluded following QA procedures for MEG data described in the Procedures section. Nevertheless, several low functioning participants remained in the ASD group. This resulted in a final sample size of 37 ($N=12$ typically developing and $N=25$ ASD participants). Participant characteristics for the final study sample are presented in Table 1.

All participants were administered the ADOS and ADI-R. All participants with ASD and none of the control participants met cutoff scores on the ADI-R and ADOS. The mean age of the participants was 11.47 ($SD = 3.48$) for the ASD group and 13.78 ($SD=3.57$) for the control group. For ethical reasons participants were not asked to stop medications during study participation. Participants with ASD were taking antidepressant ($N=4$), stimulant ($N=7$), antipsychotic ($N=5$), and anxiolytic ($N=3$) medications. None of the control participants were on psychoactive medications.

Procedures

Following an initial visit to obtain informed consent, participants were scheduled for a diagnostic evaluation and two additional sessions to administer the neuropsychological and social cognitive measures. Adequate breaks and practice sessions were offered, as appropriate, to minimize any potential anxiety with respect to testing procedures. Electrophysiological data were collected at a separate session following completion of the diagnostic and neuropsychological testing.

Measures

Diagnostic Assessment: The ADI-R is an extensive diagnostic interview designed to elicit information that is relevant to the diagnosis of autism (Lord, Rutter, & LeCouteur, 1994). Psychometric studies of the ADI-R have indicated good discriminant validity (Rutter, LeCouteur, & Lord, 2003) and test-retest reliability ranging from .93-.97 (Lord et al, 1993,

1994). The ADOS (Lord et al. 1989) is a semi-structured observational tool used to quantify behavior in relation to autism symptomatology. In a study of classification accuracy of the ADOS compared to consensus clinical diagnosis the ADOS effectively differentiated autism from non-spectrum disorders with specificities of .93–1.0 (Lord et al., 2000).

Assessment of Intelligence and Language: General language and IQ tests were administered to ensure that relevant findings were not artifacts of language or general intellectual ability. The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003), the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008), or the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002) were administered to determine age-scaled full-scale intelligence quotients. Language ability was assessed on the Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-4; Semel, Wiig, & Secord, 2003), a comprehensive language battery, to derive an overall age-scaled language quotient based on a normative sample.

Assessment of Vocal Affect Recognition: The ability to judge emotional content in speech was assessed using the Child and Adult Paralanguage subtests of the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2; Nowicki & Duke, 1994; Nowicki, 2010). The DANVA-2 paralanguage subtests are computer-administered measures that test the ability to identify emotional content in the same semantically neutral statement (i.e., *I'm going out of the room now, but I'll be back later*) spoken with different emotional inflections (i.e., happy, sad, angry, or fearful) for 24 stimuli in each condition (child or adult voices). Reliability assessment of the DANVA-2 paralanguage subscale has resulted in a Chronbach's alpha coefficient of 0.77 and retest reliability of $r = 0.74$ at four weeks post testing (Nowicki & Duke, 1994). Age scaled standard scores were derived for each subtest based on the total number of errors and then a standard score composite was derived from the average of the two standard scores.

Assessment of Cortical Auditory Processing: Auditory evoked fields were collected during a Rapid Auditory Processing Test. This test is designed to evaluate the ability of the brain to process sounds presented in rapid succession. There were six types of trials in this task, including: (a) two designed to assess magnitude and latency of basic auditory response (each consisting of a single 50ms-long tone of either 500 or 1000Hz); (b) two designed to assess sensory gating (each consisting of two identical 50ms-long tones, of either 500Hz or 1000Hz, presented 300ms apart); and (c) two designed to assess rapid auditory processing (each consisting of two different 50ms-long tones, 500Hz-1000Hz or 1000Hz-500Hz, with an inter-tone-interval of 300ms).

Electrophysiological Evaluation Procedures—MEG was used to evaluate cortical electrophysiological processing in relationship to auditory stimuli. Data were collected using a 306-channel biomagnetometer system (VectorView, Elekta, Oy, Helsinki). The system consists of an array of planar gradiometers and magnetometers, distributed at 102 spatial positions with one magnetometer and a pair of orthogonal planar gradiometers at each location. The unit can be operated in sitting and supine positions. Prior experience with

children with ASD showed that head position is more stable when data are recorded in the supine position, so this strategy was adopted for the present study. Prior to testing, four small coils were placed on the head. A 3D-digitizer was used to define a head-centered coordinate frame (using the nasion and peri-auricular points), and the position of the coils within the frame. During testing, the coils were energized and localized by the sensor array in a manner that defines the position of each sensor relative to the head. Because the MEG task involved only passive exposure to auditory stimuli, participants were allowed to watch a movie without sound while in the scanner (Edgar et al., 2013, 2014; Oram Cardy et al., 2008; Roberts et al., 2008, 2012). Unpublished pilot work in our laboratory indicated that the presence of a silent, background movie does not change latency or amplitude parameters of auditory evoked responses for either neurotypical (N=5) or ASD (N=8) subjects, although it does increase the signal-to-noise ratio (SNR) in both groups by reducing head movements and eye blinks, allowing for retention of more epochs.

A 10% hamming window was applied to each individual tone. All stimuli were presented at peak amplitude of 75 dB SPL through loudspeakers. Prior to testing, hearing thresholds were determined for each subject via pure tone audiometry, with a few subjects showing increased thresholds in one or the other ear, especially at 500 Hz. We therefore considered individualized adjustment of sound levels, but rejected this strategy because our team and others have found that magnitude and latency of behavioral and physiological responses to supra-threshold stimuli are not predicted by auditory thresholds, especially for ASD subjects. For example, many subjects with an ASD show atypical behavioral loudness growth curves for supra-threshold sounds, in the absence of altered auditory thresholds (Jones et al., 2009; Khalfa et al., 2004). It therefore seemed more prudent to standardize the physical stimulus, rather than to arbitrarily try to standardize loudness with respect to individualized threshold levels or supra-threshold perceptions. In considering this, it is also noteworthy that this same strategy was used by in a highly relevant study (Lerner et al., 2013). Different types of trials were presented in random order, 75 times each, with an inter-trial-interval of 2000 milliseconds.

Raw data were collected with a 1000 Hz digitization rate with a 0.1 – 300 Hz bandwidth. Signal space separation with temporal extension (Taulu & Hari, 2009) was used to remove artifacts from distant noise sources. Artifacts from more proximal noise sources such as eye blink and heartbeat were removed using signal space projections (SSP) defined by visual inspection of the data. Single trial epochs with a baseline of 250ms and a post-stimulus duration of 1000ms were then generated. Average evoked responses were generated for each condition (i.e., single tones – 500Hz and 1000Hz; same tone pairs – 500Hz followed by 500Hz, and 1000Hz followed by 1000Hz; and different tone pairs – 500Hz followed by 1000Hz, and 1000Hz followed by 500Hz). Prior to averaging, individual epochs were rejected if they contained large artifacts ($> 2pT$) or visual inspection evidence of residual eye blinks, eye movements, or head movements. All data sets retained a minimum of 65 out of the 75 trials. The average number of included trials did not significantly differ between the typically developing (N=72) and ASD groups (N=71). Average responses were baseline corrected and subjected to additional band-pass filtering (1-30 Hz).

Exploratory analyses using dipole modeling of the M1n response in each hemisphere indicated that differences in source localization for the 500 and 1000Hz tones were small (less than 5 mm) and inconsistent across participants. To maximize the SNR for the M1n response, data within a condition (single tone, same tone pairs, and different tone pairs) were collapsed to yield average responses for basic auditory processing (single tones), sensory gating (same tone pairs), and rapid auditory processing (different tone pairs). In addition, a supra-average response, based on all data (regardless of condition), was calculated to maximize the SNR for the M1n response to first tones (which were present in all conditions).

For each hemisphere, for each subject, the M1n was identified as the first post-stimulus magnetic peak associated with field pattern consistent with a negative evoked potential at Cz. All but 6 subjects had simultaneous multi-channel EEG, which allowed for confirmation that the identified M1n was indeed the neuromagnetic counterpart of the EEG identified N1. It is noteworthy that, for some subjects, the M1n latency was quite long (>170ms). For our purposes, we used these values, but it should be noted that many other studies have defined a M1n latency window which would not have captured these responses (e.g., Edgar et al., 2014; Roberts et al., 2008). Those studies, would have considered these subjects not to have an M1n response, rather than accepted responses with such long latencies.

In each hemisphere, a dipole source was placed in the temporal lobe and its position and orientation were optimized (using the Neuromag Xfit program), on a case-by-case basis, over a 50 millisecond window spanning the peak latency of the corresponding hemisphere's M1n response. A spherical head model was used in the calculations, with simultaneous optimization of left and right hemisphere dipole parameters. Several factors contribute to goodness-of-fit (GoF) parameters for the dipole fit. These include the signal-to-noise ratio across all sensors included in the fit. Many studies use restricted arrays of 30-90 sensors for dipole fitting, a situation that gives rise to very high GoF values. Here, all of the 306 sensors (both gradiometers and magnetometers) were included in dipole fitting process, so dipole solutions with a GoF > 70% were initially accepted. Dipole fit coordinates were then additionally checked to assure that source locations corresponded to the superior temporal peri-sylvian region (Thin-slice, 3D T1-weighted MRI data were available for all participants). These quality assurance steps resulted in exclusion of five ASD (two due to fit < 70% and three due to poor localization) and three control participants due to poor localization. For the remaining participants, GoF ranged from 70.84-96.10 ($M = 85.39$, $SD = 6.51$) for the ASD group and 71.19-94.00 ($M = 82.38$, $SD = 6.83$) for controls. Groups did not differ in GoF, $t(35) = 1.30$, $p = .20$. In all cases, we also performed a quick check of the source model using a restricted sensor array – 30 triplets aligned about the superior temporal plane – and in all cases the corresponding GoF exceeded 92% of the variance.

The resultant dipole model was taken to provide the best estimate of the M1n source location and orientation in each hemisphere. This model was then held fixed and for each participant source waveforms for single tones, same tone pairs, and different tone pairs were generated by 'passing' that condition's average evoked response through the individual participant's fixed model. This is the equivalent of the source space projection method described by Tesche et al. (1995) and Wilson et al. (2008).

There were several waveform variables of potential interest. For this project, we focused on the amplitude and latency of the M1n response to initial tones, in each hemisphere, and the overall quality of response to the second tone (T2) in pairs of same and different tones. In studies of neurotypical adults it is relatively straightforward to calculate T1/T2 amplitude ratios for M1n responses; however, for children with an ASD, there is extensive inter-participant variability in waveform morphology, with additional intra-participant variability in waveform morphology for T1 and T2. Given this, it was necessary to utilize an alternative measure to capture the overall quality of the second response. Therefore, zero lag cross correlation coefficients (CCs) were calculated to measure agreement between auditory responses in the single tone versus two tones conditions for the 300-600ms time window with higher values indicating greater agreement and lower values indicating poor agreement between waveforms.

For individuals with intact rapid processing, when two different tones are presented in rapid succession (i.e., 300ms apart) the resultant waveform demonstrates two strong responses (one to the first, and one to the second tone). The relationship between the waveforms in the two different tones condition versus the single tone condition ($CC_{\text{Single vs Different}}$) will be weak, as there are two auditory responses in the former and only one in the latter, resulting in a low CC (See top of Figure 1a). When rapid processing is impaired, however, the response to the second tone is very small or absent, and thus, the waveform looks very similar to the waveform in the single tone condition (Bottom of Figure 1a). That is to say, poor rapid auditory processing is characterized by a high value of $CC_{\text{Single vs Different}}$. For statistical evaluations, the Fisher's z transformation of $CC_{\text{Single vs Different}}$ was the variable used to quantify rapid auditory processing.

In contrast, when tones are identical with a short inter-tone-interval (e.g., less than 500 milliseconds), neurotypical subjects show a significantly reduced (gated) response to the second tone relative to the first (Top of Figure 1b). In individuals who can process rapidly-presented auditory information, intact sensory gating results in a high CC between single and same conditions ($CC_{\text{Single vs Same}}$), because there should be smaller response to the second tone of a same tone pair. In an individual with impaired sensory gating, there is a large response to both first and second tones, so there is a low $CC_{\text{Single vs Same}}$. The Fisher's z transformation of $CC_{\text{Single vs Different}}$ was subtracted from $CC_{\text{Single vs Same}}$ and the difference score was used as the variable to quantify sensory gating. This difference score was chosen over the actual z-transformed $CC_{\text{Single vs Same}}$ because it corrects for high values of $CC_{\text{Single vs Same}}$ due to impaired rapid processing rather than good sensory gating. CC analyses were conducted using SPSS Version 20. For each condition (single versus two same or two different tones), the amplitudes of the right and left source waveforms were extracted in 5 millisecond steps. Single and dual response waveforms were then compared within each hemisphere's 300-600ms time window to yield separate CC values for right and left hemisphere responses.

Statistical Analyses

First, correlations were performed to determine if variability in hearing thresholds was associated with M1n response amplitudes. Next, because cross correlation coefficient values

(CCs) were used to quantify sensory gating and rapid processing, these scores were transformed to Fisher's Z before being subject to further analysis in order to correct for the non-normality of the r distribution. Then, to evaluate whether there were significant group differences in cortical measures of auditory processing after correcting for the slightly older age of the control group, analyses of covariance (ANCOVAs) were performed for M1n response amplitudes and latencies as well as z-transformed measures of sensory gating and rapid auditory processing. Because age-scaled scores were used for all cognitive measures, it was not necessary to covary age and therefore independent samples t-tests were performed to examine group differences for these tasks. Then, finally, to test the hypothesis that auditory processing differences are related to deficits in vocal affect recognition in ASD, hierarchical regression analyses (modeled separately for each hemisphere) were performed for the ASD group. Prior evidence suggests that affect recognition abilities may be related to language skills (Boucher, Lewis, & Collis, 2000; Mazefsky & Oswald, 2007; O'Connor, 2007). Further, while age scaled standard scores were computed for the DANVA-2 to address developmental skill acquisition in vocal affect recognition (Bölte & Poustka, 2003), basic auditory processing also continues to develop throughout childhood (Gage, Siegel, & Roberts, 2003). Therefore, to control for their effects, age and CELF Core Language scores were entered into step one of the hierarchical regression analyses. MEG auditory processing variables were entered in step two of the analysis, including M1n response (1) amplitude and (2) latency, (3) the z-transformed cross correlation coefficient of the 300-600ms waveform of the single versus different condition (for rapid auditory processing), and (4) the difference score between the z-transformed cross correlation coefficients of the 300-600ms waveforms of the single versus same and single versus different conditions (for sensory gating).

Results

In support of the use of fixed supra-threshold stimulus intensities for all subjects, individual hearing thresholds were not significantly associated with right ($r=.240$ for 500Hz and $r=.238$ for 1000Hz) or left hemisphere M1n response amplitudes ($r=.062$ for 500Hz and $r=.296$ for 1000Hz). Notably, the direction of these associations was positive, indicating that lower hearing thresholds (better hearing) were very weakly associated with smaller amplitude values. Thus, the data do not suggest that weaker peripheral hearing had any effect of suppressing M1n amplitudes in the present study.

Table 2 compares groups on age, cognitive and language abilities, vocal affect recognition, and auditory processing. The broad range of language and cognitive abilities in the sample is noteworthy because both very high and low functioning participants were included to obtain an appropriately representative sample of individuals on the autism spectrum. While there were no significant differences in age $t(35) = -1.88$, $p = .07$, the control group scored significantly higher than the ASD group on tests of language, $t(32.92) = -5.47$, $p < .001$, partial $\eta^2 = .28$, intellectual ability, $t(35) = -4.16$, $p < .001$, partial $\eta^2 = .31$, and vocal affect recognition, $t(34.95) = -3.70$, $p = .001$, partial $\eta^2 = .22$. After the effects of age were covaried, M1n response latencies were significantly longer for the ASD group compared to controls in both right, $F(1,34) = 4.57$, $p = .04$, partial $\eta^2 = .12$, and left hemispheres, $F(1,34) = 5.10$, $p = .03$, partial $\eta^2 = .13$. Also, the ASD group showed impaired rapid processing in the left hemisphere compared to controls, $F(1,34) = 4.59$, $p = .04$, partial $\eta^2 = .12$. Figure 2

provides representative profiles of intact versus impaired rapid processing waveforms and their associated z-transformed cross correlation values. Significant differences were not detected in bilateral auditory response amplitudes, sensory gating, or right hemisphere rapid processing.

Preliminary analyses examining correlations between variables entered in the regression model for the ASD group are presented in Table 3. Although Full Scale Intelligence Quotients (FSIQ) suggested that general intellectual ability in the ASD group was lower than age-based expectations (which was expected given our efforts to include lower functioning participants), FSIQ was not entered into step 1 of the regression analysis due to its high correlation with language ability, another control variable. Inclusion of only one of these variables in our model allowed us to reduce multicollinearity within the model. Likewise, there were several significant correlations between MEG auditory processing variables and their counterpart in the contralateral hemisphere. As such, separate regression models were run for each hemisphere to further minimize multicollinearity.

Results of hierarchical regression analyses indicated that the control variables (age and language ability) accounted for a significant proportion of the variance in DANVA-2 Vocal Affect Recognition Scores for both the left and right hemisphere models, $R^2 = .46$, $F(2,22) = 9.24$, $p = .001$. This suggests that the linear combination of age and language functioning are related to the ability to recognize emotional content from non-semantic vocal cues. MEG auditory processing variables were then added to the models at step two. In the left hemisphere model, MEG measures of auditory processing accounted for an additional 27.1% of the variance in vocal affect recognition (R^2 change = .27, $F(4,18) = 4.48$, $p = .01$). In the right hemisphere model, these variables accounted for an additional 31.8% of the variance in vocal affect recognition ($R^2 = .32$, $F(4,18) = 6.34$, $p = .002$), indicating that auditory processing was significantly associated with vocal affect recognition abilities in participants with ASD, even after controlling for the effects of age and language ability. Beta coefficients and collinearity statistics for the independent variables are presented in Table 4. Multicollinearity values were within acceptable ranges, with tolerance values (proportion of variance in the independent variable that cannot be accounted for by the other independent variables) $.450$ and variance inflation factors ($VIF = 1/\text{tolerance}$) < 2.22 .

T-tests on beta weights indicate that longer M1n response latency and poor rapid auditory processing were significantly associated with poor vocal affect recognition performance for both the right and left hemisphere models. These values did not achieve statistical significance for M1n amplitude or sensory gating variables, but these null findings should be viewed with caution given that these analyses were only powered to detect extremely large effects (due to the number of independent variables in the model and relatively small sample size). Figure 3 presents partial regression plots of the association between each auditory processing variable and vocal affect recognition controlling for the effects of all other independent variables.

Discussion

This was the first study to use MEG to assess auditory evoked fields in relation to social-emotional skills in children and adolescents with autism. The primary aims were to determine the relationship between autism-related deficits in vocal affect recognition and MEG-based measures of auditory processing including M1n latency and amplitude, CC-based indices of sensory gating, and CC-based measures of rapid auditory processing. Results indicated that individuals with ASD show delayed auditory response latency and impairments in rapid auditory processing and vocal affect recognition compared to neurotypical participants. Further, these deficits in latency and auditory processing were significantly related to performance on a vocal affect recognition task, even after controlling for age and language ability. These results provide preliminary support for the hypothesis that abnormalities in basic auditory processing are associated with deficits in decoding affect from non-semantic vocal cues in individuals with ASD.

Vocal Affect Recognition in ASD

Results of the present study are consistent with previous literature identifying deficits in vocal affect recognition for individuals with ASD (Golan et al., 2006; Järvinen-Pasley et al., 2008; Lindner & Rosén, 2006). Such deficits have not been universally reported, with at least two prior studies failing to identify vocal affect recognition deficits in ASD (although both showed deficits on a face-to-voice affect matching task, Boucher et al., 2000; O'Connor, 2007). In the later study, deficits in vocal affect recognition were selectively intact for adult participants diagnosed with Asperger's Disorder (see also Mazefsky & Oswald, 2007). Notably, the main distinguishing factors between a diagnosis of high functioning autism and Asperger's Disorder are a history of language or cognitive delay for those diagnosed with autism and no history of these delays for those diagnosed with Asperger's Disorder. This relationship between vocal affect recognition and general language abilities is supported by bivariate correlation analyses in the present study. In fact, there is also prior evidence that some individuals with ASD may use verbal mediation to compensate for difficulty interpreting non-semantic cues (Golan et al., 2006; Lindner & Rosén, 2006). This suggests that vocal affect recognition deficits may originate from difficulties processing the auditory cues that convey emotion or from deficits in the higher order interpretation of their meaning. Notably, the vocal affect recognition stimuli for the task used in the present study consisted of the same semantically neutral statement expressed in different emotional inflections, thus precluding the use of verbal mediation strategies.

Electrophysiological Indices of Auditory Processing and Vocal Affect Recognition in ASD

Results of the present study also are consistent with previous research indicating that relative to neurotypical control subjects, individuals with ASD show (a) delayed auditory evoked responses (Oram Cardy et al., 2008; Roberts et al., 2010, 2011) and (b) impaired rapid auditory processing in the left hemisphere (Cardy et al., 2005) compared to neurotypical controls. Significant group differences were not detected on measures of M1n amplitude, sensory gating, or right hemisphere rapid processing.

It has been argued that there are three main sub-processes involved in vocal affect comprehension: (1) analysis of the acoustic cues of vocalization; (2) derivation of emotional significance from these auditory cues; and (3) integration of emotional significance with higher order cognitive processes (Schirmer & Kotz, 2006). In considering social/emotional dysfunction in autism, it is often assumed that these difficulties reflect a breakdown of sub-processes two and three; however, emerging data suggest that basic auditory processing as embodied in sub-process one is a major contributor to vocal affect recognition abilities. Results of the present study suggest that variability in the basic cortical processing of auditory sensory information is related to deficits in vocal affect recognition in ASD beyond that accounted for by the effects of age and language abilities.

Regression models including the age, language ability, and electrophysiological measures of basic auditory processing accounted for a large amount of the total variance in vocal affect recognition (77.4% for the right hemisphere model and 72.8% for the left hemisphere model). Of that variance, MEG variables accounted for a substantial proportion of the variance (31.8% in the right and 27.1% in the left hemisphere models). This suggests that difficulties in the analysis of acoustic cues may contribute to difficulty in vocal affect recognition for affected individuals on the autism spectrum.

Despite prior evidence that abnormal auditory processing may be associated with some of the core deficits in ASD, the present study was the first to examine electrophysiological responses to basic auditory stimuli information (i.e., pure tone evoked responses) specifically in relation to auditory social cue recognition performance. Our results complement previous findings identifying abnormalities in processing elements of speech associated with emotional content, such as prosody, in individuals with ASD (Järvinen-Pasley et al., 2008). Specifically, the present study suggests that latency of the M1n response and the ability to process rapidly presented basic auditory information are associated with vocal affect recognition. It is noteworthy that both of these measures are related to temporal processing of auditory information, which has been one of the most robust finding of auditory processing abnormalities in individuals with ASD (Gage, Siegel, Callen, & Roberts, 2003; Oram Cardy et al., 2008; Roberts et al., 2010, 2011).

In fact, in a recent study examining event-related potentials (ERPs) while participants performed the same vocal affect recognition task described in the current study, N100 auditory response latencies (associated with the early perceptual components of auditory processing) were associated with errors on the vocal affect recognition task of the DANVA-2 (Lerner et al., 2013). Also consistent with the present study, N100 response amplitudes were not significantly associated with vocal affect recognition; however, these null findings in the present study cannot be interpreted given that the analyses were only powered to detect extremely large effects. The findings from the present study also suggest that the auditory perceptual deficits associated with vocal affect recognition skills are related to not only processing of complex speech utterances but also to more basic sound perception, including auditory processing of pure tones.

The present study identified a relationship between longer M1n response latency and poor vocal affect recognition. This finding is consistent with a previous study by Gage, Siegel,

and Roberts (Gage, Siegel, & Roberts, 2003) who found that M100 response latencies were longer for a group of children and adolescents with autism compared to similarly aged control participants, and while hemispheric differences were not statistically significant, there was a trend for longer response latencies in the left hemisphere compared to right. Dunn et al. (1999) also identified delayed left hemisphere N100 latencies in children with autism compared to age-matched controls. Oram Cardy et al. (2008), however, reported an association between right hemisphere M50 and M100 response latencies and language ability across children with autism, Asperger's Syndrome, specific language impairment, and typically developing children. In the present study the association between right and left hemisphere response latencies was very strong ($r=.98$), and both were significantly related to vocal affect recognition.

Impaired rapid auditory processing also was related to weaker performance on the vocal affect recognition task in this study. This finding is consistent with results from a study by Oram Cardy et al. (2005), who reported a failure to respond to the second tone of a rapid tone processing task in children and adolescents with autism and impaired language and in participants with specific language impairment in the absence of autism. In contrast, the majority of participants with intact language showed intact response to the second tone. The authors posited that these results may indicate that impaired rapid auditory processing in the left hemisphere is related to language impairment, consistent with early work demonstrating rapid auditory processing deficits in individuals with specific language impairment (Tallal & Piercy, 1973, 1974, 1975). Results of the present study suggest that these findings may be extended to social aspects of language when rapid auditory processing is impaired in either hemisphere or bilaterally. M1n amplitudes and sensory gating variables were not significantly associated with vocal affect recognition in either model, and while these null findings are consistent with some previous work (Oranje et al., 2013), they must be interpreted with caution in the context of the extremely limited power of the present study given the sample size and number of independent variables in the regression models. These results suggest that the ability to respond to and efficiently process rapidly presented auditory information may be important in extracting affective cues from speech, and for individuals on the autism spectrum, impairment in these abilities may contribute to difficulty in vocal affect recognition.

Limitations and Future Directions

Several limitations of this study must be acknowledged. First, the individual regression models were only powered to detect very large effects. Therefore, null findings cannot be interpreted; however, despite the limitations in power, the effect size for the relationship between auditory processing and vocal affect recognition was sufficiently large to identify a significant relationship for some of the measures of auditory processing evaluated in this study. Replication of these results in a larger sample will be necessary to draw conclusions about which auditory processes may be most strongly associated with vocal affect recognition. Second, because there were six different conditions in the auditory processing task only 75 trials were presented for each condition. This was done in an effort to keep the task duration low in order to facilitate inclusion of lower functioning participants. Following artifact removal this resulted in insufficient number of trials to generate averages with

reasonable signal to noise ratios. Thus conditions between low and high tones were collapsed to increase signal to noise (e.g., single low and single high tone conditions were collapsed to a single tone condition). This resulted in an inability to examine effects separately for 500Hz versus 1000Hz tones and prior work has identified longer response latencies to these lower tones in the left, but not right hemisphere for individuals with ASD (Gage, Siegel, Callen, et al., 2003). These previous findings suggest that collapsing high and low tone conditions may have differentially impacted the left hemisphere response latencies. Thus, given this differential impact, as well as the separate models for right versus left hemisphere auditory processing, lateralization of findings (specifically lack thereof) in the present study must be interpreted with caution. Also, although consistent with methodology in prior MEG studies of auditory processing in individuals with ASD (e.g., Edgar et al., 2013, 2014; Oram Cardy et al., 2008; Roberts et al., 2008), the impact of playing a silent movie on these results is unknown. Because this method was applied to both groups, however, there is no reason for concern regarding any differential impact in the present study.

The present study examined the relationship between general rates of errors in vocal affect recognition and temporal processing of auditory information in ASD. These findings warrant examination of the relationship between error rates in identification of specific affective conditions and the cortical response to auditory cues that characterize that specific emotion, such as increased intensity for anger or spectral noise for sadness (Schirmer & Kotz, 2006). Future studies should expand upon the auditory processing tasks involved in the current study to explore the contribution of other aspects of auditory processing to perception of other vocal affective states (e.g., volume perception, tone discrimination, processing of spectral noise, etc.). More comprehensive assessment of both auditory and higher order cognitive processes involved in the judgment of vocal affect should be incorporated into future models.

Finally, the results of this study identified an association between atypical auditory processing and impairment in vocal affect recognition; however, these data were cross-sectional. Longitudinal research is necessary to explore causal directions for these relationships and to further understand the developmental process involved in the acquisition of these deficits. Considering the early developmental onset of ASD, dysfunction in the sensory systems which are often apparent very early in life (Baranek, 1999; Dahlgren & Gillberg, 1989), precedes development of higher order social cognitive skills. Given our current findings, longitudinal tracking of symptom emergence and relationships between symptoms may reveal an etiological contribution of early sensory dysfunction to aberrant social development in autism. Such a finding would suggest that sensory dysfunction may be an important target for early intervention in ASD, as early remediation could theoretically minimize symptom emergence.

Conclusions

The findings from the present study are consistent not only with a growing body of research identifying relationships between atypical low-level processing and social abilities, but also with the theoretical framework of the Research Domain Criteria initiative to identify

alternative classification methods based on continuous dimensions of traits, behavior, and neurobiology to identify mechanisms of psychopathology. Given the early emergence of ASD symptomatology, consideration of the neurodevelopmental context of this sensory processing dysfunction may be key if we are to understand the impact it has on other developing processes (Casey, Oliveri, & Insel, 2014). Thus, these findings may have implications for incorporation of sensory-based interventions in addressing social perceptual deficits or early intervention efforts in sensory processing to prevent symptom emergence. Specifically, treatments targeting remediation of delays in auditory response latency or impairments in rapid auditory processing may have an impact on other domains of functioning, including auditory social perception.

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References

- Abrams DA, Lynch CJ, Cheng KM, Phillips J, Supekar K, Ryali S. Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *PNAS*. 2013; 110(29):12060–12065.10.1073/pnas.1302982110 [PubMed: 23776244]
- Adamson A, Hare AO, Graham C. Impairments in Sensory Modulation in Children with Autistic Spectrum Disorder. *British Journal of Occupational Therapy*. 2006; 69(8):357–364.
- Adolphs R. The neurobiology of social cognition. *Current Opinion in Neurobiology*. 2001; 11(2):231–9. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11301245>. [PubMed: 11301245]
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) Diagnostic and Statistical Manual of Mental Disorders 4th edition TR. 2013.
- Aoki Y, Yahata N, Watanabe T, Takano Y, Kawakubo Y, Kuwabara H, et al. Yamasue H. Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain : A Journal of Neurology*. 2014; 137:3073–3086.10.1093/brain/awu231 [PubMed: 25149412]
- Baranek GT. Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *Journal of Autism and Developmental Disorders*. 1999; 29(3): 213–24. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10425584>. [PubMed: 10425584]
- Baron-Cohen S, Ring Ha, Bullmore ET, Wheelwright S, Ashwin C, Williams SC. The amygdala theory of autism. *Neuroscience and Biobehavioral Reviews*. 2000; 24(3):355–64. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10781695>. [PubMed: 10781695]
- Bölte S, Poustka F. The recognition of facial affect in autistic and schizophrenic subjects and their first-degree relatives. *Psychological Medicine*. 2003; 33(5):907–15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12877405>. [PubMed: 12877405]
- Boucher J, Lewis V, Collis GM. Voice processing abilities in children with autism, children with specific language impairments, and young typically developing children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2000; 41(7):847–57. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11079427>.
- Brock ME, Freuler A, Baranek GT, Watson LR, Poe MD. Temperament and sensory features of children with autism. *Journal of Autism and Developmental Disorders*. 2012; 42(11):2271–2284. Temperament. 10.1007/s10803-012-1472-5 [PubMed: 22366913]
- Cardy JEO, Flagge CAEJ, Roberts W, Brian J, Roberts TPL. Magnetoencephalography identifies rapid temporal processing deficit in autism and language impairment. *Neuroreport*. 2005; 16(4):329–332. [PubMed: 15729132]

- Crick NR, Dodge Ka. A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin*. 1994; 115(1):74–101.10.1037//0033-2909.115.1.74
- Dahlgren SO, Gillberg C. Symptoms in the first two years of life: A preliminary population study of infantile autism. *European Archives of Psychiatry & Neurological Science*. 1989; 238:169–174.
- Demopoulos C, Hopkins J, Lewine JD. Relationships between Nonverbal and Verbal Social Cognitive Skills and Complex Social Behavior in Children and Adolescents with Autism. Under Review.
- Dunn M, Vaughan H Jr, Kreuzer J, Kurtzberg D. Electrophysiologic Correlates of Semantic Classification in Autistic and Normal Children. *Developmental Neuropsychology*. 1999; 16(1):79–99.10.1207/S15326942DN160105
- Edgar JC, Khan SY, Blaskey L, Chow VY, Rey M, Gaetz W, et al. Roberts TPL. Neuromagnetic Oscillations Predict Evoked-Response Latency Delays and Core Language Deficits in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. 2013; 10.1007/s10803-013-1904-x
- Edgar JC, Lanza MR, Daina AB, Monroe JF, Khan SY, Blaskey L, et al. Roberts TPL. Missing and delayed auditory responses in young and older children with autism spectrum disorders. *Frontiers in Human Neuroscience*. 2014; 8(June):417.10.3389/fnhum.2014.00417 [PubMed: 24936181]
- Gage NM, Siegel B, Callen M, Roberts T. Cortical sound processing in children with autism disorder : an MEG investigation. *Neuroreport*. 2003; 14(16):2047–2051.10.1097/01.wnr.0000090030.46087 [PubMed: 14600495]
- Gage NM, Siegel B, Roberts TPL. Cortical auditory system maturational abnormalities in children with autism disorder: an MEG investigation. *Brain Research Developmental Brain Research*. 2003; 144(2):201–9. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12935917>. [PubMed: 12935917]
- Gandal MJ, Edgar JC, Ehrlichman RS, Mehta M, Roberts TPL, Siegel SJ. Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biological Psychiatry*. 2010; 68(12):1100–6.10.1016/j.biopsych.2010.09.031 [PubMed: 21130222]
- Globerson E, Amir N, Kishon-rabin L, Golan O. Prosody recognition in adults with high-functioning autism spectrum disorders: From psychoacoustics to cognition. *Autism Research*. 2014; 1–11.10.1002/aur.1432
- Golan O, Baron-Cohen S, Hill J. The Cambridge Mindreading (CAM) Face-Voice Battery: Testing complex emotion recognition in adults with and without Asperger syndrome. *Journal of Autism and Developmental Disorders*. 2006; 36(2):169–83.10.1007/s10803-005-0057-y [PubMed: 16477515]
- Greenspan SI, Wieder S. Developmental Patterns and Outcomes in Infants and Children with Disorders in Relating and Communicating : A Chart Review of 200 Cases of Children with Autistic Spectrum Diagnoses. *The Journal of Developmental and Learning Disorders*. 1997; 1(1): 1–38.
- Järvinen-Pasley A, Heaton P. Evidence for reduced domain-specificity in auditory processing in autism. *Developmental Science*. 2007; 10(6):786–93.10.1111/j.1467-7687.2007.00637.x [PubMed: 17973796]
- Järvinen-Pasley A, Peppé S, King-Smith G, Heaton P. The relationship between form and function level receptive prosodic abilities in autism. *Journal of Autism and Developmental Disorders*. 2008; 38(7):1328–40.10.1007/s10803-007-0520-z [PubMed: 18172749]
- Jones CRG, Happé F, Baird G, Simonoff E, Marsden AJS, Tregay J, et al. Charman T. Auditory discrimination and auditory sensory behaviours in autism spectrum disorders. *Neuropsychologia*. 2009; 47(13):2850–8.10.1016/j.neuropsychologia.2009.06.015 [PubMed: 19545576]
- Khalfa S, Bruneau N, Rogé B, Georgieff N, Veuillet E, Adrien JL, et al. Collet L. Increased perception of loudness in autism. *Hearing Research*. 2004; 198(1-2):87–92.10.1016/j.heares.2004.07.006 [PubMed: 15617227]
- Lerner MD, McPartland JC, Morris JP. Multimodal emotion processing in autism spectrum disorders: an event-related potential study. *Developmental Cognitive Neuroscience*. 2013; 3:11–21.10.1016/j.dcn.2012.08.005 [PubMed: 23245216]

- Lindner JL, Rosén La. Decoding of emotion through facial expression, prosody and verbal content in children and adolescents with Asperger's syndrome. *Journal of Autism and Developmental Disorders*. 2006; 36(6):769–77.10.1007/s10803-006-0105-2 [PubMed: 16639533]
- Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, Schopler E. Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*. 1989; 19(2):185–212. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2745388>. [PubMed: 2745388]
- Lord C, Rutter M, Le Couteur a. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*. 1994; 24(5):659–85. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7814313>. [PubMed: 7814313]
- Mayes SD, Calhoun SL. Symptoms of Autism in Young Children and Correspondence with the DSM. *Infants and Young Children*. 1999; 12(2):90–97.
- Mazefsky, Ca; Oswald, DP. Emotion perception in Asperger's syndrome and high-functioning autism: the importance of diagnostic criteria and cue intensity. *Journal of Autism and Developmental Disorders*. 2007; 37(6):1086–95.10.1007/s10803-006-0251-6 [PubMed: 17180461]
- McCann J, Peppé S. Prosody in autism spectrum disorders: a critical review. *International Journal of Language & Communication Disorders / Royal College of Speech & Language Therapists*. 2003; 38(4):325–350.10.1080/1368282031000154204 [PubMed: 14578051]
- Nowicki, S. Manual for the receptive tests of the Diagnostic Analysis of Nonverbal Accuracy 2. Atlanta, GA: 2010.
- Nowicki S, Duke MP. Individual differences in the nonverbal communication of affect: The diagnostic analysis of nonverbal accuracy scale. *Journal of Nonverbal Behavior*. 1994; 18(1):9–35.10.1007/BF02169077
- O'Connor K. Brief report: impaired identification of discrepancies between expressive faces and voices in adults with Asperger's syndrome. *Journal of Autism and Developmental Disorders*. 2007; 37(10):2008–13.10.1007/s10803-006-0345-1 [PubMed: 17273935]
- Oram Cardy JE, Flagg EJ, Roberts W, Roberts TPL. Delayed mismatch field for speech and non-speech sounds in children with autism. *Neuroreport*. 2005; 16(5):521–5. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15770164>. [PubMed: 15770164]
- Oram Cardy JE, Flagg EJ, Roberts W, Roberts TPL. Auditory evoked fields predict language ability and impairment in children. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*. 2008; 68(2):170–5.10.1016/j.ijpsycho.2007.10.015 [PubMed: 18304666]
- Oranje B, Lahuis B, van Engeland H, Jan van der Gaag R, Kemner C. Sensory and sensorimotor gating in children with multiple complex developmental disorders (MCDD) and autism. *Psychiatry Research*. 2013; 206(2-3):287–92.10.1016/j.psychres.2012.10.014 [PubMed: 23164481]
- Pelphrey K, Adolphs R, Morris JP. Neuroanatomical substrates of social cognition dysfunction in autism. *Mental Retardation and Developmental Disabilities Research Reviews*. 2004; 10(4):259–71.10.1002/mrdd.20040 [PubMed: 15666336]
- Potter D, Summerfelt A, Gold J, Buchanan RW. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. *Schizophrenia Bulletin*. 2006; 32(4):692–700.10.1093/schbul/sbj050 [PubMed: 16469942]
- Roberts TPL, Cannon KM, Tavabi K, Blaskey L, Khan SY, Monroe JF, et al. Edgar JC. Auditory magnetic mismatch field latency: a biomarker for language impairment in autism. *Biological Psychiatry*. 2011; 70(3):263–9.10.1016/j.biopsych.2011.01.015 [PubMed: 21392733]
- Roberts TPL, Heiken K, Kahn SY, Qasmieh S, Blaskey L, Solot C, et al. Edgar JC. Delayed magnetic mismatch negativity field, but not auditory M100 response, in specific language impairment. *Neuroreport*. 2012; 23(8):463–8.10.1097/WNR.0b013e32835202b6 [PubMed: 22551948]
- Roberts TPL, Khan SY, Rey M, Monroe JF, Cannon K, Woldoff S, et al. Edgar JC. MEG detection of delayed auditory evoked responses in Autism Spectrum Disorders: Towards an imaging biomarker for autism. *Autism Research*. 2010; 3(1):8–18.10.1002/aur.111.MEG [PubMed: 20063319]
- Roberts TPL, Schmidt GL, Egeth M, Blaskey L, Rey MM, Edgar JC, Levy SE. Electrophysiological signatures: magnetoencephalographic studies of the neural correlates of language impairment in

- autism spectrum disorders. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*. 2008; 68(2):149–60.10.1016/j.ijpsycho.2008.01.012 [PubMed: 18336941]
- Rogers SJ, Hepburn S, Wehner E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *Journal of Autism and Developmental Disorders*. 2003; 33(6):631–42. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14714932>. [PubMed: 14714932]
- Schirmer A, Kotz Sa. Beyond the right hemisphere: brain mechanisms mediating vocal emotional processing. *Trends in Cognitive Sciences*. 2006; 10(1):24–30.10.1016/j.tics.2005.11.009 [PubMed: 16321562]
- Schmidt GL, Rey MM, Oram Cardy JE, Roberts TPL. Absence of M100 source asymmetry in autism associated with language functioning. *Neuroreport*. 2009; 20(11):1037–41.10.1097/WNR.0b013e32832e0ca7 [PubMed: 19491710]
- Semel, E.; Wiig, E.; Secord, W. *Clinical Evaluation of Language Fundamentals-Fourth Edition (CELF-IV)*. San Antonio, TX: The Psychological Corporation; 2003.
- Shapiro EG, Hughes SJ, August GJ, Bloomquist ML. Processing of emotional information in children with Attention-Deficit Hyperactivity Disorder. *Developmental Neuropsychology*. 1993; 9(3 & 4): 207–224.
- Tallal P, Piercy M. Developmental aphasia: impaired rate of non verbal processing as a function of sensory modality. *Neuropsychologia*. 1973; 11:389–398.10.1016/0028-3932(73)90025-0 [PubMed: 4758181]
- Tallal P, Piercy M. Developmental aphasia: rate of auditory processing and selective impairment of consonant perception. *Neuropsychologia*. 1974; 12:83–93.10.1016/0028-3932(74)90030-X [PubMed: 4821193]
- Tallal P, Piercy M. Developmental aphasia: the perception of brief vowels and extended stop consonants. *Neuropsychologia*. 1975; 13:69–74.10.1016/0028-3932(75)90049-4 [PubMed: 1109463]
- Taulu S, Hari R. Removal of magnetoencephalographic artifacts with temporal signal-space separation: demonstration with single-trial auditory-evoked responses. *Human Brain Mapping*. 2009; 30(5):1524–34.10.1002/hbm.20627 [PubMed: 18661502]
- Tecchio F, Benassi F, Zappasodi F, Gialloreti LE, Palermo M, Seri S, Rossini PM. Auditory sensory processing in autism: a magnetoencephalographic study. *Biological Psychiatry*. 2003; 54(6):647–654.10.1016/S0006-3223(03)00295-6 [PubMed: 13129660]
- Tesche CD, Uusitalo Ma, Ilmoniemi RJ, Huottilainen M, Kajola M, Salonen O. Signal-space projections of MEG data characterize both distributed and well-localized neuronal sources. *Electroencephalography and Clinical Neurophysiology*. 1995; 95(3):189–200. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7555909>. [PubMed: 7555909]
- Tomchek S, Dunn W. Sensory processing in children with and without autism: A comparative study using the Short Sensory Profile. *The American Journal of Occupational Therapy*. 2007; 61(2):190–200. [PubMed: 17436841]
- Wechsler, D. *Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III)*. San Antonio, TX: Pearson Assessments; 2002.
- Wechsler, D. *Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV)*. San Antonio, TX: Pearson Assessments; 2003.
- Wechsler, D. *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)*. San Antonio, TX: Pearson Assessments; 2008.
- Wilson, TW.; Hernandez, OO.; Asherin, RM.; Teale, PD.; Reite, ML.; Rojas, DC. *Cerebral Cortex*. Vol. 18. New York, N.Y.: 2008. Cortical gamma generators suggest abnormal auditory circuitry in early-onset psychosis; p. 371-8.1991
- Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biological Psychiatry*. 2007; 62(3):192–7.10.1016/j.biopsych.2006.07.002 [PubMed: 16950225]

Rapid Processing: CC_{Single} vs Different

Intact Rapid Processing

Impaired Rapid Processing

Gating: $CC_{\text{Single vs Same}} - CC_{\text{Single vs Different}}$

Single vs Same

Single vs Different

Figure 1.

Quantification of rapid processing and gating variables from cross correlations (CC) of source waveforms in single tone and two tones conditions. Boxes show tone type and stimulus onset. (a) The rapid auditory processing condition is quantified by taking the cross correlation between the source waveforms at 300-600ms in the two different tones condition (i.e., response to the second tone) versus the single tone condition (i.e., no second tone so no

auditory response at 300-600ms). For intact rapid processing (top timecourse) there is low agreement between these two waveforms because one demonstrates an auditory response to a tone and one does not, resulting in a low CC coefficient. In contrast, when rapid processing is impaired (i.e., no or weak response to the second tone) there is higher agreement between the two waveforms (bottom timecourse), resulting in a high CC coefficient. (b) The 300-600ms response in the two same tones condition looks similar to the response in the single condition, even though a second tone is presented (top timecourse), resulting in high waveform agreement and a high CC coefficient. When a high $CC_{\text{Single vs Same}}$ is achieved for a participant who is able to process both tones (i.e., intact rapid processing, or low $CC_{\text{Single vs Different}}$), sensory gating is intact. Therefore, sensory gating was quantified by subtracting $CC_{\text{Single vs Different}}$ (the CC coefficient for rapid processing; bottom timecourse) from $CC_{\text{Single vs Same}}$ (top timecourse). High $CC_{\text{Single vs Same}} - \text{Low } CC_{\text{Single vs Different}} = \text{Higher difference value} = \text{better sensory gating}$. Use of this difference score prevents mistaking impaired rapid processing (i.e., inability to process rapidly presented tones) for intact gating.

Figure 2. Examples of source waveforms from one control participant and two participants with ASD. Data are shown for conditions when there is a single tone, two tones that are the same, and two tones that are different. Boxes indicate tone types and onset. For the control participant there is a clear response to the tone, with the response complete by 250 milliseconds. In the different condition, there is a strong response to the second tone indicative of good rapid auditory processing. The response in the same condition looks almost identical to the response in the single condition, even though a second tone is presented. In the context of this participant's intact rapid processing this indicates good sensory gating. The activity profile of the first ASD participant is similar to that of the control. The second ASD participant shows some impairment in rapid processing. Cross correlation values for these participants across conditions are presented below.

Figure 3.

Relationships between Vocal Affect Recognition and Cortical Auditory Processing Adjusting for All Other Independent Variables. For each plot the vertical axis represents the residual values after regressing vocal affect recognition on all independent variables other than the variable identified in the horizontal axis. The horizontal axis represents the residual values after regressing the specified independent variable on all other independent variables.

Table 1
Participant Demographics for Final Study Sample (N)

	ASD (N=25)	Control (N=12)
Ethnicity		
Caucasian	17	5
Hispanic	3	4
Asian	2	1
African American	1	0
Multiracial	2	2
Gender		
Male	18	7
Female	7	5
Handedness		
Right	18	9
Left	3	3
Ambidexterous	1	0
Unknown	3	0
Diagnostic Category		
Asperger's Disorder	8	
Autistic Disorder	15	
PDD-NOS	2	

Table 2
Group Comparisons for Cognitive and MEG Auditory Processing Measures

	ASD		Control	
	M ± SD	(Range)	M ± SD	(Range)
Participant Characteristics				
Age	11.47 ± 3.48	(5.5-18.5)	13.78 ± 3.57	(8-18.92)
FSIQ	84.16 ± 19.82	(46-136)	111.08 ± 14.92	(93-144)
PRI/PIQ	94.96 ± 18.50	(53-133)	106.92 ± 14.78	(86-131)
VCI/VIQ	88.56 ± 22.40	(50-142)	117.33 ± 16.29	(93-150)
CELF Core	82.04 ± 26.22	(40-126)	114.08 ± 9.02	(99-133)
Expressive	83.24 ± 25.58	(45-126)	112.67 ± 9.68	(101-132)
Receptive	84.48 ± 23.14	(45-128)	108.25 ± 11.57	(92-134)
DANVA-2	91.06 ± 11.75	(71-108)	101.42 ± 5.28	(96-109)
MEG Auditory Processing Measures ^d				
Amp R	28.98 ± 21.32	(1.30-94.40)	24.51 ± 24.58	(.30-71.00)
Amp L	30.12 ± 34.87	(.60-168.80)	25.79 ± 24.25	(7.50-91.30)
Latency R	161.08 ± 60.08	(95-260)	110.42 ± 9.40	(90-125)
Latency L	161.64 ± 60.08	(100-260)	110.83 ± 9.49	(90-125)
Gating R	.00 ± .32	(-.58-.71)	-.03 ± .37	(-.65-.64)
Gating L	.05 ± .40	(-.64-.80)	.05 ± .35	(-.36-.94)
Rapid R	.18 ± .43	(-.48-1.43)	-.09 ± .34	(-.60-.47)
Rapid L	.10 ± .49	(-1.18-1.05)	-.28 ± .30	(-.73-.29)

* p<05

** p=001

*** p<001

[†] Corrected values—Equal variances not assumed

^a Age entered as covariate into ANCOVA because MEG data are not norm-referenced

Note: Age-scaled standard scores (M=100, SD=15 for normative sample) were used for all cognitive measures and thus age was not covaried in these analyses.

Table 3
Correlations between Regression Model Variables in ASD Group

	Age	CELF	IQ	Danva	Amp R	Amp L	Latency R	Latency L	Gating R	Gating L	Rapid R
Age	-										
CELF	.17	-									
IQ	.05	.87***	-								
DANVA	-.12	.63***	.65***	-							
Amp R	-.23	-.17	-.01	-.22	-						
Amp L	-.45*	-.02	.11	-.15	.75***	-					
Latency R	-.56***	.07	.15	-.15	.37	.50*	-				
Latency L	-.55***	.12	.22	-.11	.38	.52***	.98***	-			
Gating R	-.30	.00	.12	.24	.15	.03	.13	.12	-		
Gating L	-.55***	-.15	-.23	-.12	.11	.30	.53***	.50*	.38	-	
Rapid R	-.03	.08	.11	-.11	-.27	-.06	-.29	-.29	-.09	-.10	-
Rapid L	-.26	-.30	-.28	-.33	-.01	.32	-.11	-.11	-.16	.01	.54***

* p < .05

** p < .01

*** p < .001

Table 4
Regression Models of Auditory Processing on Vocal Affect Recognition in ASD

Model	B	SeB	β	Tolerance	VIF
Left Hemisphere					
Step 1 ($R^2 = .46$) **					
Age	-.80	.54	-.24	.97	1.03
Language	.30	.07	.67***	.97	1.03
Step 2 (R^2 change = .27) *					
Age	-2.44	.59	-.72**	.49	2.03
Language	.31	.06	.69***	.84	1.19
L Min Latency	-.11	.04	-.55**	.45	2.22
L Amplitude	-.01	.05	-.03	.58	1.71
L Gating	-3.76	4.56	-.13	.62	1.62
L Rapid Processing	-8.90	3.63	-.37*	.67	1.49
Right Hemisphere					
Step 1 ($R^2 = .46$) **					
Age	-.80	.54	-.24	.97	1.03
Language	.30	.07	.67***	.97	1.03
Step 2 (R^2 change = .32) **					
Age	-2.09	.52	-.62**	.54	1.87
Language	.36	.05	.80***	.86	1.16
R Min Latency	-.13	.03	-.64**	.50	1.98
R Amplitude	-.06	.07	-.11	.79	1.26
R Gating	4.24	4.42	.12	.87	1.15
R Rapid Processing	-11.11	3.43	-.41**	.79	1.26

* $p < .05$

** $p < .01$

*** $p < .001$